PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 908 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2005/003186	International filing date *(day/month/year)* 24.03.2005	Priority date *(day/month/year)* 26.03.2004
International Patent Classification (IPC) or both national classification and IPC INV. A61K9/51		
Applicant CELL THERAPEUTICS EUROPE S.R.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2006	29.08.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Felder, C Telephone No. +49 89 2399-7852

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2005/003186

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-11 as originally filed

Claims, Numbers

1-6 as originally filed

Claims, Pages

1-6 filed with telefax on 25.01.2006

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 6

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 6

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 93/05768 A (MEDAC GESELLSCHAFT FUER KLINISCHE SPEZIALPRAEPARATE) 1 April 1993 (1993-04-01)

D2: WO 94/20072 A (PHARMACIA AB; WESTESEN, KIRSTEN; SIEKMANN, BRITTA) 15 September 1994 (1994-09-15)

D3: M.A. EGEA, M.A. ALSINA, M. ESPINA, O.VALLS, M.L. GARCIA: "Penetration kinetics of cis-diamminedichloroplatinum II loaded nanoparticles in lipid monolayers as a membrane model of the reticuloendothelial system" THIN SOLID FILMS, vol. 210/211, 1992, XP002340125 Sequoia

D4: US-B1-6 596 889 (MENTA ERNESTO ET AL) 22 July 2003 (2003-07-22)

D5: US-A-6 011 166 (VALSECCHI ET AL) 4 January 2000 (2000-01-04)

D6: US 520 236 A (M.R. GASCO) 5 October 1993 (1993-10-05)

The present application discloses solid lipid nanoparticles (SLN) of platinum compounds characterized by anionic ligands and ligands containing amino groups and a method of production of said SLN's.

Claim 6 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

1. Novelty

The present application does meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-5 is new in the sense of Article 33(2) PCT.

None of the cited documents **D1-D6** discloses (citations see ISR) solid lipid nanoparticles characterized by anionic ligands and ligands containing amino groups further containing platinum compounds, more particularly of antitumour platinum complexes.

Therefore, the subject-matter of the present claims 1-5 is novel over the prior art.

2. Inventive step

The present application does meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-5 does involve an inventive step in the sense of Article 33(3) PCT.

The problem to be solved by the present invention may therefore be regarded as finding a way to prepare SLN's characterized by anionic ligands and ligands containing amino groups containing platinum compounds. None of the cited documents suggest the preparation of such SLN's characterized by anionic ligands and ligands containing amino groups with platinum compounds.

Therefore, the subject-matter of the present claims 1-5 involves an inventive step.

3. Industrial applicability

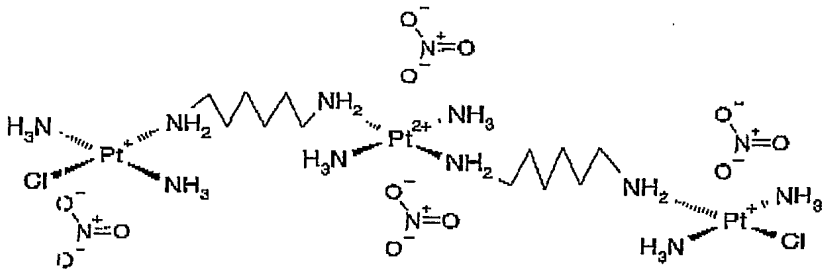
For the assessment of the present claim 6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Present claims 1-5 are industrial applicable.

CLAIMS

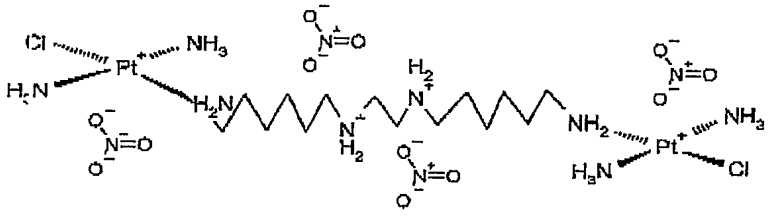
1. Solid Lipid Nanoparticles of a platinum complex characterized by anionic ligands and ligands containing amino groups.

2. Solid Lipid Nanoparticles of a platinum complex according to claim 1 selected from trans-{bis[trans(diammine)(chloro)platinum (II) (μ-1,6-hexanediamine)]}diammineplatinum tetranitrate salt of formula I



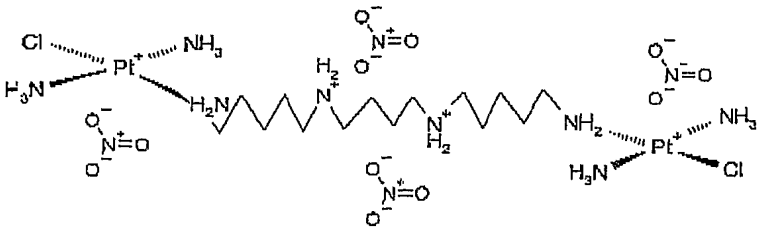
Formula I

bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-7,10-diazahexadecane-N1,N16) dinitrate salt. $2HNO_3$ of formula II,



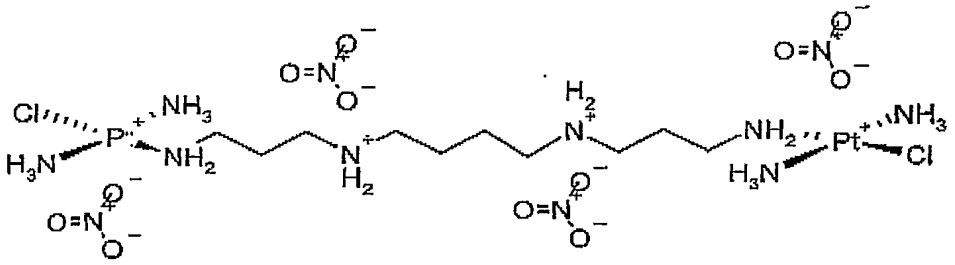
Formula II

bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-6,11-diazahexadecane-N1,N16) dinitrate salt. $2HNO_3$ of formula III,



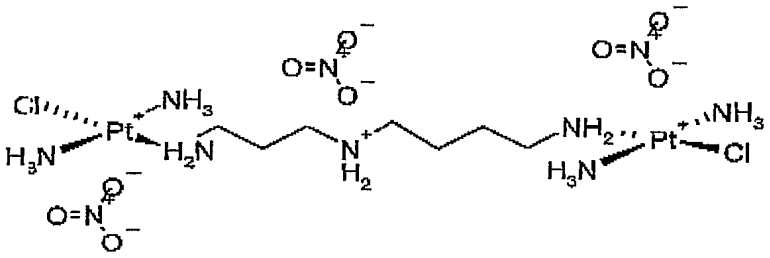
Formula III

bis{trans(diammine)(chloro)platinum(II)}-μ-(1,12-diamino-4,9-diazadodecane-N_1,N_{12}) dinitrate salt. $2HNO_3$ of formula IV,



Formula IV

bis{trans(diammine)(chloro)platinum (II)}-μ-(1,8-diamino-4-azaoctane-N^1,N^8) dinitrate salt. HNO_3 of formula V,



Formula V

3. Solid Lipid Nanoparticles according to claim 1 or 2 obtainable by a process comprising :

a) preparing a first microemulsion by mixing a molten lipid, a surfactant, and optionally a co-surfactant and the platinum compound acqueous solution;

b) preparing a solution by mixing a surfactant and optionally a co-surfactant in water, heating to complete solution, preferably at the same melting temperature of the lipid used in a) and adding a co-surfactant;

c) dispersing the microemulsion obtained in a) into the solution obtained in b) obtaining a multiple microemulsion c);

d) dispersing the microemulsion obtained in c) in aqueous medium at a temperature ranging from 0.5°C to 4°C obtaining a dispersion of solid lipid microspheres;

e) washing with aqueous medium through ultrafiltration the obtained lipid microspheres obtained in d) and lyophilizing, optionally in the presence of a bulking agent and of a cryoprotecting agent.

4. A process for the preparation of Solid Lipid Nanoparticles of claims 1-2, comprising:

a) preparing a first microemulsion by mixing a molten lipid, a surfactant, and optionally a co-surfactant and the platinum compound acqueous solution;

b) preparing a solution by mixing a surfactant and optionally a co-surfactant in water, heating to complete solution, preferably at the same melting temperature of the lipid used in a) and adding a co-surfactant;

c) dispersing the microemulsion obtained in a) into the solution obtained in b) obtaining a multiple microemulsion c);

d) dispersing the microemulsion obtained in c) in aqueous medium at a temperature ranging from 0.5°C to 4°C obtaining a dispersion of solid lipid microspheres;

e) washing with aqueous medium through ultrafiltration the obtained lipid microspheres obtained in d) and lyophilizing, optionally in the presence of a bulking agent and of a cryoprotecting agent.

5. Pharmaceutical compositions comprising the solid lipid nanoparticles of claims 1-3.

6. A method of treating patients affected by cancer sensitive to platinum complexes which comprises administering to said patients a therapeutically effective amount of the solid lipid nanoparticles of claims 1-3.